Leptospirosis

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Leptospirosis

- An emerging infectious disease
- Significant morbidity in military personnel deployed in tropical areas
  - Mortality remains significant due to delay in diagnosis due to lack of infrastructure and adequate clinical suspicion.
  - Pulmonary hemorrhage is an increasingly common manifestation of sever disease (pathology unknown)
- A zoonosis of ubiquitous distribution, but more common in the tropics
- Clinical manifestations can mimic those of malaria and viral hemorrhagic fevers, which merits attention with current concerns of bioterrorism.

Clinical Features

- “A disease of protean manifestations”
- Can be an asymptomatic illness, to mild/moderate/severe febrile disease, to severe icteric fatal disease.
- How the diverse types of disease develop is not currently understood (host vs. organism factors??)

- Anicteric Leptospirosis
- Icteric Leptospirosis

Anicteric Leptospirosis

- The great majority of infections have this manifestation.
- Typically subclinical or mild in presentation.
- Majority of recognized cases present with a mild febrile illness of sudden onset.
- HA (severe), myalgias, abdominal pain, conjunctival suffusion, biphasic fever (fever may recur 3-4 days after initial resolution)
  - Conjunctival suffusion and muscle tenderness (specifically calf and lumbar area) can be distinguishing features
- 2-3 weeks of symptoms

Anicteric Leptospirosis

- **Aseptic meningitis**—occurs in up to 25% of cases, more so in younger patients
  - Slightly elevated opening pressure, elevated protein, normal glucose, and lymphocytic pleocytosis
- **Differential Dx**—common viral infections (influenza), HIV seroconversion, typhoid, rickettsial, EBV, brucella, malaria, viral hepatitis

Icteric Leptospirosis (Weil's Disease)

- More severe disease, may be rapidly fatal
- Mortality rate is 5-15%
- 5-10% of leptospirosis infections are the icteric form
- Labs show significantly elevated bilirubin (30-40 mg/dL), moderately elevated transaminases
- Complications include
  - Non-oliguric acute renal failure (16-40%), thrombocytopenia, and pulmonary involvement included pulmonary hemorrhage
  - Cardiac involvement includes pericarditis
  - Ocular involvement includes uveitis
  - Spontaneous abortion can occur in pregnancy
  - Chronic infection can occur similar to Lyme

Icteric Leptospirosis (Weil's Disease)

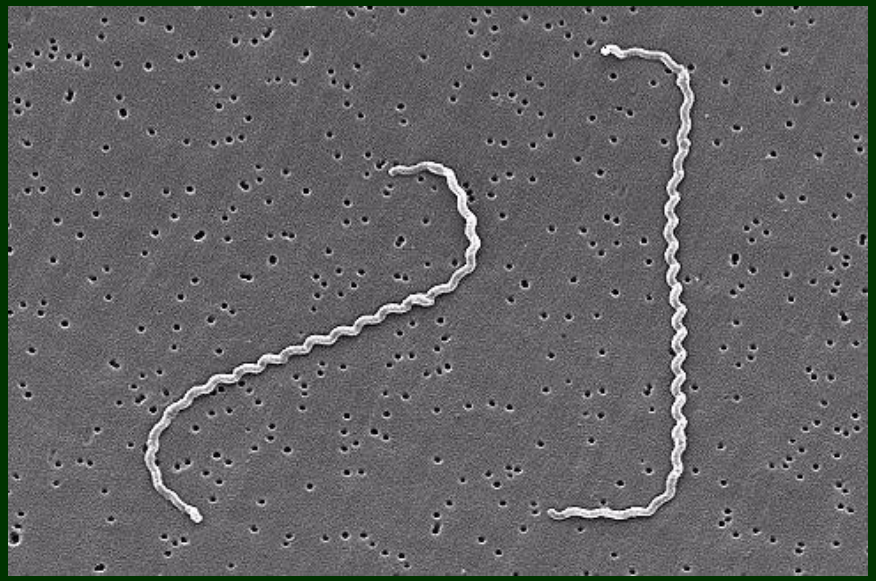
- Mortality predictors
  - Oliguric renal failure (OR 9.0)
  - With Pulmonary involvement
    - Hemodynamic disturbance (OR 6.0)
    - Elevated serum creatinine concentration>265 umol/L (OR 10.6)
    - Serum potassium >4 mmol/L (OR 19.9)

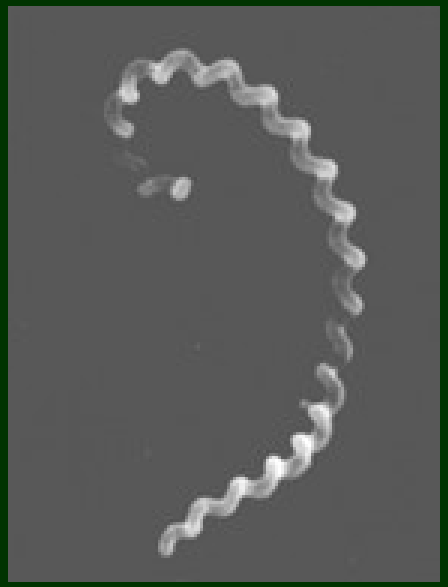
Historical Interest

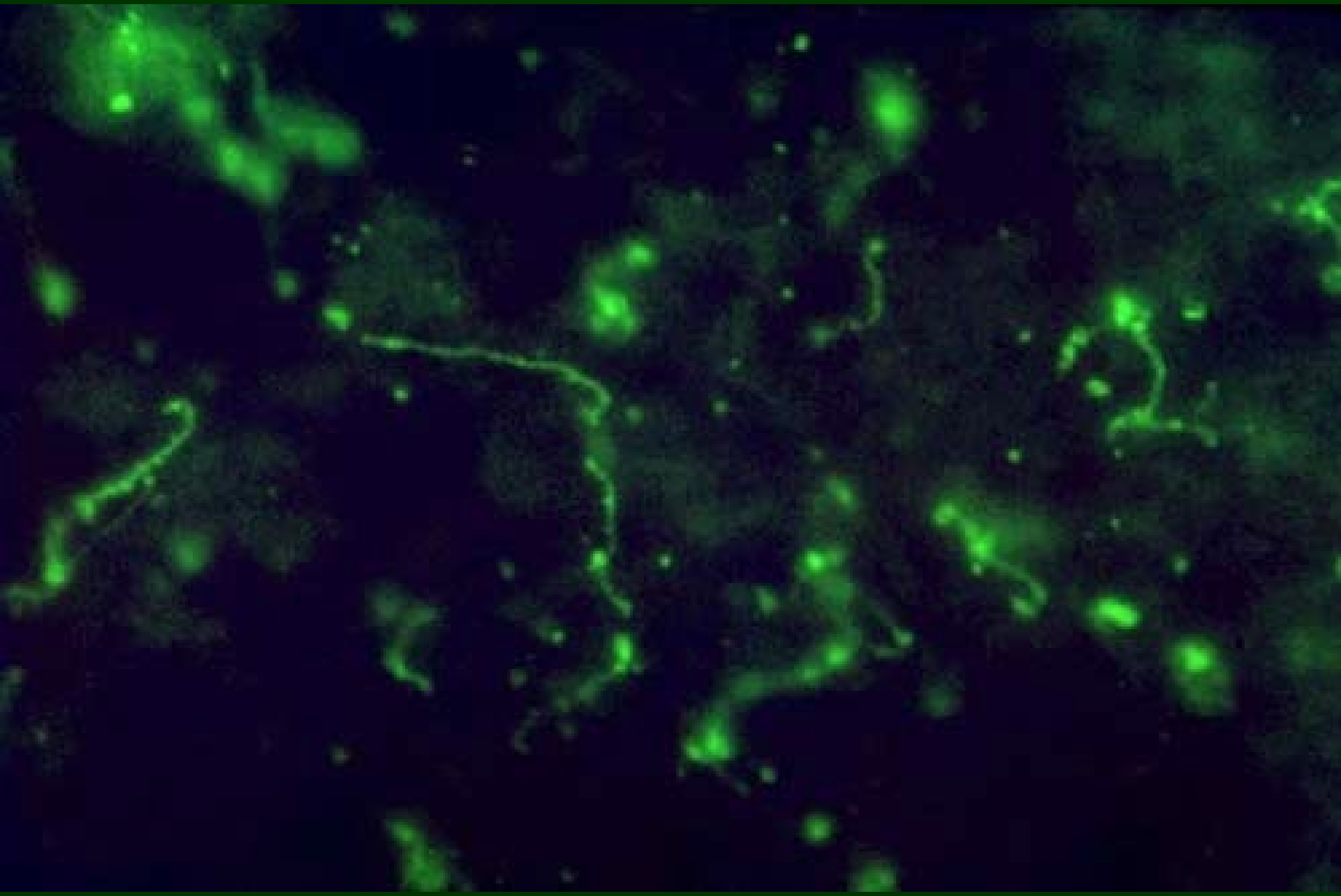
- **Weil's disease**—Adolf Weil described a syndrome of severe disease (icteric leptospirosis with renal failure) in the late 1800's
- Occupational hazard in sewer workers in late 1800's
- Associated with rice harvesting in ancient China
- Role of the rat in human infection described in early 1900's

Microbiology

- Leptospires are highly coiled spirochetes
- Visualized under dark field microscopy
- Are obligate aerobes, and grow best at 28-30^{o}C
- In culture, these grow very slowly, and should only be read as negative at 12-16 weeks







Microbiology

- Before 1989 the genus *Leptospira* was divided in two species
  - *L. interrogans* (all pathogenic strains)
  - *L. biflexa* (saprophytic strains from the environment)
- Both divided into multiple serovars grouped into serogroups
- Serovars antigenically related
- More recently classified based on molecular techniques based on genotypes
  - This is not an antigenic classification and confuses some
  - Not grouped based on pathogenic/non-pathogenic strains
  - overlap

Epidemiology

- Most widespread zoonosis in the world
- Source of human infection
  - **Direct contact with infected animal**
  - **Indirect contact with urine of infected animal**
- Incidence is higher in warm climates than in temperate regions
- Disease is seasonal (peaks summer/fall of temperate regions)
- Highest incidence in USA is in HI
- Not a notifiable disease in the USA (1994)

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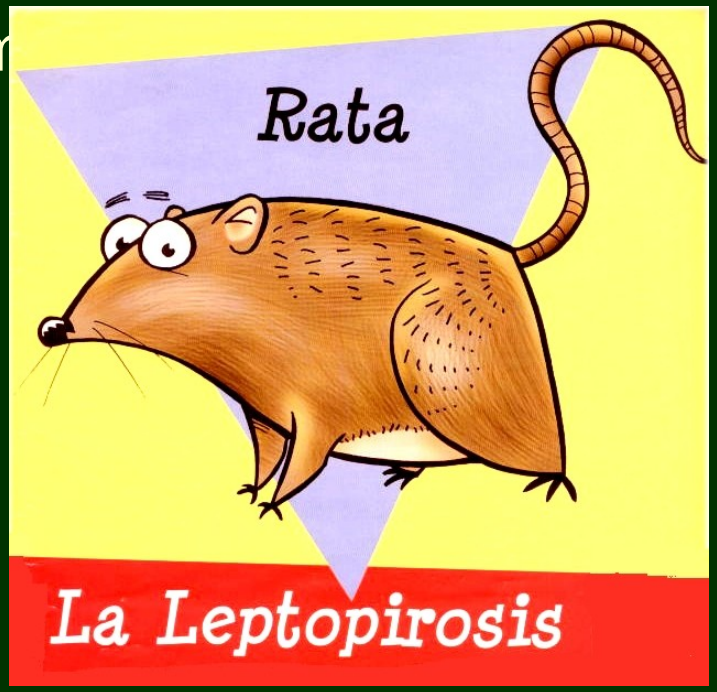
SWIM OR HIKE AT YOUR OWN RISK
FOR MORE INFORMATION CALL
HAWAII DEPARTMENT OF HEALTH

Epidemiology (continued)

- Usual portal of entry is skin abrasion or conjunctiva
- Animal bites
- Direct transmission between humans is rare
- Mammals (including hum
  - Maintenance host
  - Accidental (incidental) hosts



Maintenance Hosts

- In maintenance hosts the disease is maintained in the proximal renal tubule and shed in the urine
  - Typical maintenance hosts include small rodents or dogs
  - Organisms can be shed in a symptom free animal for a lifetime
  - Specific animal populations may maintain specific serovars
- 41 of 500 healthy Kansas dogs had leptospiruria
- 22% of 1200 slaughte
  leptospiral antibodies
  positive urine)

Human Infection occurs with...

1) Occupational exposure
   - Farmers, vets, abattoir workers, meat inspectors, rodent animal control, sewer workers, miners
2) Recreational exposure
   - Water sports, canoeing, white water rafting, freshwater swimming or fishing, waterfalls
3) Avocational exposure
   - Gardening with bare hands, walking barefoot, contaminated drinking water

Diagnosis

- Nonspecific labs include elevated ESR, bilirubin, transaminases, alk phos. UA shows pyuria, proteinuria, hematuria.
- May develop a leukocytosis (left shift).
  - Contrast to Dengue which has atypical lymphocytosis
- Culture will definitively diagnose but is difficult
  - Need dark field microscopy
  - Slow growing
  - Leptospiremic only during first week of illness, usually prior to onset of symptoms
  - Urine culture positive 2-3 weeks into illness
  - Send cultures in heparin or sodium oxalate tubes, not in citrate as it is inhibitory

Diagnosis--Serological

- Most cases are diagnosed in this manner
- AB present in serum 5-7 days after onset of Sx
- **MAT—microscopic agglutination test**
  - Patient's serum with a live antigen suspension of leptospirosis serovars
  - Must examine under dark field microscopy, and correct titer determined
  - Complex test
- Paired sera to confirm the diagnosis
  - 4 fold increase in titers
  - Single elevated titer of >200 or >800 or >1600 depending on endemicity at location

Alternate Diagnostic Methods

- ELISA (rapid test for IgM, 45 minutes)
- Complement fixation titers
- Macroscopic slide agglutination
- PCR
  - Currently at research laboratories
  - Need to complete PCR for specific serovars

Treatment

- Some may argue none at all as most infections spontaneously resolve.
- Symptomatic therapy for anicteric infection
- More severe infection can be treated with PCN or doxycycline
- Ceftriaxone also reported as beneficial
- A Jarisch-Herxheimer reaction has been reported

Susceptibility Testing Research at BAMC

	Range	MIC_{50}	MIC_{90}
Doxycycline	**0.05-6.25**	**0.39**	**1.56**
Penicillin G	**0.02-25**	**1.56**	**6.25**
Erythromycin	**≤0.01**	**≤0.01**	**≤0.01**
Azithromycin	**≤0.01-0.05**	**≤0.01**	**0.02**
Clarithromycin	**≤0.01**	**≤0.01**	**≤0.01**
Telithromycin	**≤0.01**	**≤0.01**	**≤0.01**
Chloramphenicol	**0.78-6.25**	**3.13**	**6.25**

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Penicillin G	**0.02-6.25**	**1.56**	**6.25**
Doxycycline	**0.05-6.25**	**0.39**	**1.56**
Ciprofloxacin	**≤0.01-0.2**	**0.05**	**0.2**
Moxifloxacin	**≤0.01-0.2**	**0.1**	**0.2**
Levofloxacin	**≤0.01-0.1**	**0.1**	**0.1**
Gatifloxacin	**≤0.01-0.05**	**0.02**	**0.05**
BMS-284756	**≤0.01-0.05**	**≤0.01**	**0.02**

Full Macrolide and Ketolide BAMC Results

Table 1

	Doxycycline	Penicillin G	Erythromycin	Azithromycin	Clarithromycin	Telithromycin	Chloramphenicol
L. biflexa/ Andamana	0.05	6.25	<0.01	<0.01	<0.01	<0.01	0.78
*L. interrogans/*Australis	0.20	1.56	<0.01	<0.01	<0.01	<0.01	0.78
L. interrogans/ Australis	0.39	6.25	<0.01	<0.01	<0.01	<0.01	1.56
L. interrogans/ Autumnalis	0.1	3.13	<0.01	<0.01	<0.01	<0.01	0.78
L. kirschneri/ Butembo	0.20	12.5	<0.01	<0.01	<0.01	<0.01	1.56
L. noguchii/ Fortbragg	0.39	0.10	<0.01	<0.01	<0.01	<0.01	3.13
L. borgpetersenii/ Ballum	0.39	0.78	<0.01	<0.01	<0.01	<0.01	6.25
L. interrogans/ Bataviae	0.20	0.39	<0.01	0.02	<0.01	<0.01	3.13
L. interrogans/ Canicola	0.39	3.13	<0.01	0.05	<0.01	<0.01	3.13
L. weilii/ Celledoni	0.20	1.56	<0.01	<0.01	<0.01	<0.01	1.56
L. kirschneri/ Cynopteri	1.56	12.5	<0.01	0.05	<0.01	<0.01	6.25
L. interrogans/ Djasiman	0.39	0.39	<0.01	0.02	<0.01	<0.01	6.25
L. interrogans/ Grippotyphosa	0.39	0.39	<0.01	<0.01	<0.01	<0.01	6.25
L. santarosai/ Borincana	3.13	0.10	<0.01	<0.01	<0.01	<0.01	6.25
L interrogans/ Hebdomadis	0.39	0.39	<0.01	0.02	<0.01	<0.01	3.13
L. interrogans/ Copenhageni	0.10	0.10	<0.01	<0.01	<0.01	<0.01	0.78
L. interrogans/ Icterohaemorrhagiae	0.20	3.13	<0.01	<0.01	<0.01	<0.01	1.56
L. interrogans/ Mankarso	0.78	3.13	<0.01	<0.01	<0.01	<0.01	6.25
L. santarosai/ Georgia	0.20	0.10	<0.01	<0.01	<0.01	<0.01	3.13
L. interrogans/ Pomona	6.25	0.39	<0.01	<0.01	<0.01	<0.01	12.5
L. santarosai/ Alexi	0.78	3.13	<0.01	<0.01	<0.01	<0.01	6.25
L. interrogans/ Pyrogenes	0.20	0.02	<0.01	<0.01	<0.01	<0.01	1.56
L. interrogans/ Hardjo	0.20	3.13	<0.01	<0.01	<0.01	<0.01	3.13
L. interrogans/ Wolffi	0.20	1.56	<0.01	<0.01	<0.01	<0.01	3.13
L. santarosai/ Shermani	0.78	3.13	<0.01	<0.01	<0.01	<0.01	6.25
*L. biflexa/*Patoc	0.78	6.25	<0.01	<0.01	<0.01	<0.01	3.13

Prophylaxis

- Doxycycline 200 mg once a week
- Especially for military and adventure travelers
- 1982—Study of US soldiers deployed to Panama
  - 940 soldiers, either Doxy or placebo
  - 4.2% in placebo group, 0.2% in Doxy group
- Vaccine is not widely available and suffers from problems
  - Unacceptable side effects of killed bacterial vaccine
  - Typically short term protection
  - Varying local patterns of *Leptospira* serovars limits protection
  - Incomplete knowledge of mechanisms of protective immunity against leptospiral infections

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